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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/557, 31/54, 9/20, 9/28 // (A61K 31/557, 31:54, 31:195)

A1

(11) International Publication Number: WO 99/65496

(43) International Publication Date: 23 December 1999 (23.12.99)

(21) International Application Number: PCT/CA99/00541

(22) International Filing Date: 10 June 1999 (10.06.99)

(30) Priority Data:
2,241,342 15 June 1998 (15.06.98) CA

(71)(72) Applicant and Inventor: SHERMAN, Bernard, Charles [CA/CA]; 50 Old Colony Road, Willowdale, Ontario M2L 2K1 (CA).

(81) Designated States: AU, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: PHARMACEUTICAL TABLETS COMPRISING AN NSAID AND A PROSTAGLANDIN

(57) Abstract

A pharmaceutical tablet which incorporates two smaller tablets, one of which comprises an NSAID and the other of which comprises misoprostol.

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
SHERMAN, Bernard Charles
150 Signet Driv
Weston, Ontario
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CANADA

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing (day/month/year)	30.03.2000
Applicant's or agent's file reference: PCT-1044	REPLY DUE: within 3 month(s) from the above date of mailing — June 30, 2000 ✓
International application No.: PCT/CA99/00541	International filing date (day/month/year): 10/06/1999
Priority date (day/month/year): 15/06/1998	
International Patent Classification (IPC) or both national classification and IPC: A61K31/557	
Applicant: SHERMAN, Bernard, Charles	

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain document cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 15/10/2000. OCT. 16, 2000

Fax 7421

Name and mailing address of the international preliminary examining authority:
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Authorized officer / Examiner
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Simm, M.D. 7411

Formalities officer (incl. extension of time limits)
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Telephone No. +49 89 2399 8072

WRITTEN OPINION International application No. PCT/CA99/00541

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-6 as originally filed

Claims, No.:

1-6 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	
Inventive step (IS)	Claims	1-8
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/CA99/00541

Re Item I
Basis of the opinion

Reference is made to the following document:

D1: US-A-5 601 843 (GIMET RENE A ET AL) 11 February 1997 (1997-02-11) cited in the application

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Inventive Step (Art 33(3) PCT)

The document D1, acknowledged on page 2 second paragraph of the present application, is considered to be the closest prior art. Claim 1 differs from the teachings of D1 in that the two tablets, one comprising an NSAID and the other comprising misoprostol, are embedded in a pharmaceutical tablet. The technical effect provided by this technical feature is that the misoprostol is protected from the environment (see page 2, lines 23-30).
The technical problem to be solved by the present application regarding the closest prior art is to provide the tablet of D1 with a protection from the environment (see page 2, lines 23-30).
The solution is to cover both tablets with a shell (see page 3, lines 21-24 and page 5, lines 11-15) which is constituted of usual tablet excipients. It appears that the skilled person in wishing to separate or protect one substance, would simply use such a coating. An example of that is shown in D1 where in order to separate both active principles an coating constituted of normal excipients is used (see Examples). Thus, this solution is considered to be obvious in respect of D1 and in view of the normal procedur s in the art.

Dependent claims 2-8 do not contain any feature which could render claim 1 inventive becaus all these features are disclosed in D1 (see claims 1 and 5) or are the results of

normal procedures in the art.

Re Item VIII

Certain observations on the international application

There is an inconsistency between the description and claims regarding apparent essential features (Art. 6 and PCT Guidelines C-III, 4.3). From the description of the present application (page 2, first paragraph) it appears that an essential feature of the present invention is that contact between both active principles must be prevented. However, this essential feature is neither reflected in claim 1 nor in the Examples.

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Correspondence with the EPO on PCT Chapter II demands

In order to ensure that your PCT Chapter II demand is dealt with as promptly as possible you are requested to use the enclosed self-adhesive labels with any correspondence relating to the demand sent to the Munich Office.

One of these labels should be affixed to a prominent place in the upper part of the letter or form etc. which you are filing.

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A1

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(54) Title: PHARMACEUTICAL TABLETS COMPRISING AN NSAID AND A PROSTAGLANDIN

(57) Abstract

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WO 99/65496

09/719142

533 Rec'd PCT/PTO 08 DEC 2000

PCT/CA99/00541

PHARMACEUTICAL TABLETS COMPRISING AN NSAID AND A PROSTAGLANDIN

BACKGROUND OF THE INVENTION

The invention herein is directed to a pharmaceutical tablet which comprises both an NSAID and misoprostol.

Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise a class of drugs which have long been recognized as having high therapeutic value especially for the treatment of inflammatory conditions such as exhibited in inflammatory diseases like osteoarthritis and rheumatoid arthritis. While the NSAIDs present a beneficial therapeutic value, they also exhibit undesirable side effects. An especially undesirable side effect of the administration of NSAIDs is the ulcerogenic effects generally associated with chronic use. NSAID induced ulcers in the stomach can be dangerous. Such ulcers generally exhibit few or no symptoms and may cause dangerous bleeding when undetected. In some instances, bleeding ulcers can prove fatal.

Certain prostaglandins have been shown to prevent NSAID induced ulcers. Misoprostol is a prostaglandin which has been accepted for use in the treatment of NSAID induced ulcers in many countries, including the United States.

It is desirable to provide a pharmaceutical composition which exhibits the beneficial properties of an NSAID and which also exhibits the beneficial properties of misoprostol for countering the ulcerogenic side effects attendent to NSAID administration.

This can be achieved by combining an NSAID and misoprostol in a single pharmaceutical tablet. However this in not easy to do, because misoprostol is highly unstable, and it is thus desirable not to have the misoprostol and NSAID mixed together, so as to prevent any deleterious effect of the NSAID on the stability of the misoprostol.

One solution to this problem, which is disclosed in US Patent 5601843, is to produce a tablet consisting of an inner core which comprises the NSAID and a mantle which surrounds the inner core and comprises the misoprostol. It is also disclosed that, in order to prevent contact between the misoprostol and the NSAID at the surface of the inner core, the inner core may be coated with an inert coating. Such coating may be an enteric coating, which also serves to reduce the likelihood of the NSAID dissolving in the stomach and thereby prevent exposing the stomach to the NSAID.

While the invention of US Patent 5601843 accomplishes its objective of separating the NSAID from the misoprostol, it has certain disadvantages. One disadvantage is the need to have a coating on the inner core in order to completely prevent contact between the NSAID in the inner core and the misoprostol in the mantle.

A second disadvantage is that the misoprostol is dispersed throughout the mantle, and is thus exposed to the environment at the surface of the tablet. This exposure increases the vulnerability of the misoprostol to degradation due to the effects of light or atmospheric oxygen and moisture.

The object of the present invention is to enable a pharmaceutical tablet that incorporates both an NSAID and misoprostol, but overcomes these disadvantages.

BRIEF SUMMARY OF THE INVENTION

The present invention is a pharmaceutical composition in the form of a tablet in which two smaller tablets are embedded, one of which comprises an NSAID and the second of which comprises misoprostol.

DETAILED DESCRIPTION OF THE INVENTION

Pharmaceutical tablets are routinely made on a tablet press. In the tabletting process, a mixture of materials in the form of a free flowing powder or granular mix is filled into a metal die, into which a metal punch protrudes from beneath. A second metal punch is then inserted into the die from above, and pressure is applied to the upper and lower punches to cause the powder or granular mix to be compressed into a tablet. The upper punch is then withdrawn, and the tablet is ejected from the die by raising the lower punch further into the die.

Compositions (i.e. tablets) of the present invention may be made as follows:

1. Firstly, a tablet comprising the NSAID and a tablet comprising the misoprostol are made in separate tabletting operations. The portion of the composition which surrounds the two smaller tablets will be referred to herein as the "shell".

2. Then the final composition is assembled in a further tabletting operation as follows:

   (i) Part of the powder or granular mix of which the shell is to be comprised is filled into th die, into which a punch has been inserted from below.

(ii) One of the smaller tablets comprising the NSAID and one of the smaller tablets comprising the misoprostol are then inserted into the die.

(iii) The balance of the powder or granular mix of which the shell is to be comprised is then filled into the die to cover two smaller tablets.

(iv) The upper punch is then inserted into the die from above and pressure is applied between the punches to compress the powder or granular mix around the two smaller tablets into the form of the final tablet.

(v) The upper punch is then withdrawn and the lower punch is raised further into the die to eject the composition.

The NSAID contained within one of two smaller tablets will preferably be piroxicam or diclofenac or a salt of diclofenac such as diclofenac sodium or diclofenac potassium. Most preferably, the NSAID will be diclofenac sodium.

Where diclofenac or a salt thereof is used, the amount per tablet will preferably be from 25 to 75 mg. The tablet containing diclofenac or salt thereof will contain, along with the diclofenac or salt thereof, usual tablet excipients such as binders, lubricants, fillers and the like. Preferably, the tablet containing the diclofenac or salt thereof will be coated with an enteric film coating to prevent the diclofenac or salt thereof from dissolving until after it has passed through the stomach and entered the small intestine. The enteric coating can b formulated with any suitable enteric coating polymer, many of which are known to those skilled in the art.

Where piroxicam is used as the NSAID, the amount per tablet will preferably be 10 to 20 mg. Again th tablet containing piroxicam will also comprise usual tablet excipients.

The tablet containing the misoprostol will also include, along with the misoprostol, usual tabletting excipients. The misoprostol will preferably be used in the form of a dispersion in hydroxypropyl methylcellulose, which is known in the prior art to improve the stability of misoprostol. The quantity of misoprostol per tablet will preferably be about 200 µg.

The shell which surrounds the tablet containing the NSAID and the tablet containing the misoprostol will be comprised of usual tablet excipients, without any active medicinal ingredient mixed therein.

The invention will be further understood from the following example, which is intended to be illustrative and not limiting of the scope of the invention.

EXAMPLE 1

Tablets containing diclofenac sodium are made with a composition as follows:

	Amount per tablet
Diclofenac sodium	50.0 mg
Microcrystalline cellulose	24.0 mg
Magnesium stearate	1.0 mg
Croscarmellose sodium	5.0 mg
	80.0 mg

These cores ar then optionally enteric coated by spraying onto them a suspension or solution of an enteric coating polymer and a plasticiz r.

EXAMPLE 2

Tablets containing misoprostol are made with a composition as follows:

	Amount per tablet
Misoprostol 1% dispersion in hydroxypropyl methylcellulose	20.0 mg
Microcrystalline cellulose	8.5 mg
Magnesium stearate	0.5 mg
Croscarmellose sodium	1.0 mg
	30.0 mg

EXAMPLE 3

A powder mix for producing the shell of the final tablet is prepared as a mixture of 99.5% by weight microcrystalline cellulose and 0.5% magnesium stearate.

EXAMPLE 4

The final composition is then made by making tablets from the mix of Example 3 and embedding in each such tablet one tablet from Example 1 and one tablet from Example 2, by the procedure previously described; that is to say, using a tablet press equipped to insert one tablet from Example 1 and one tablet from Example 2 as well as a quantity of the powder mix for the shell from Example 3 into a die, and making the final tablet by compression between a lower punch and a upper punch inserted into the die from below and above respectively.

CLAIMS:

1. A pharmaceutical tablet in which are imbedded two smaller tablets, one of which comprises an NSAID and the other of which comprises misoprostol.

2. A pharmaceutical tablet as is Claim 1 wherein the NSAID is piroxicam.

3. A pharmaceutical tablet as in Claim 1 wherein the NSAID is selected from diclofenac and salts thereof.

4. A pharmaceutical tablet as in Claim 2, wherein the amount of piroxicam is from about 10 mg to about 20 mg.

5. A pharmaceutical tablet as in Claim 3, wherein the amount of diclofenac or a salt thereof is from about 25 mg to about 75 mg.

6. A pharmaceutical tablet as in any of Claims 1 to 5, wherein the amount of misoprostol is about 200 µg.

INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/CA 99/00541

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/557 A61K31/54 A61K9/20 A61K9/28
//(A61K31/557,31:54,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X, Y	EP 0 864 324 A (BASF AG) 16 September 1998 (1998-09-16) the whole document	1-6
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-/---

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search
16 September 1999

Date of mailing of the international search report
23/09/1999

Name and mailing address of the ISA
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Authorized officer
Fischer, H

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00541

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 99/00541

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No PCT/CA 99/00541

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PCT-1044		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00541	10/06/1999	15/06/1998
International Patent Classification (IPC) or national classification and IPC A61K31/557		
Applicant SHERMAN, Bernard, Charles		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07/01/2000	06.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d	Authorized officer Simm, M.D.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00541

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-6	as originally filed				

Claims, No.:

1-7	as received on	29/05/2000	with letter of	25/05/2000	

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-7
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: US-A-5 601 843 (GIMET RENE A ET AL) 11 February 1997 (1997-02-11) cited in the application

Inventive Step (Art 33(3) PCT)

The document D1, acknowledged on page 2 second paragraph of the present application, is considered to be the closest prior art. Claim 1 differs from the teachings of D1 in that the two tablets, one comprising an NSAID and the other comprising misoprostol, are embedded in a pharmaceutical tablet covered by material of the shell of the pharmaceutical tablet.

The technical effect provided by this technical feature is that the misoprostol is protected from the environment (see page 2, lines 23-30).
The technical problem to be solved by the present application regarding the closest prior art is to provide the tablet of D1 with a protection from the environment (see page 2, lines 23-30).

The solution is to cover both tablets with a shell (see page 3, lines 21-24 and page 5, lines 11-15) which is constituted of usual tablet excipients.

This solution is not disclosed in the cited prior art. Thus, it appears that present claim 1 is novel and involves an inventive step.

The features of dependent claims 2-8 are disclosed in D1 (see claims 1 and 5) or are the results of normal procedures in the art.

CLAIMS:

1. A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by material of the shell of the pharmaceutical tablet, one of which tablet comprises an NSAID and the other of which tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment of the surface of the pharmaceutical tablet.

2. The pharmaceutical tablet of Claim 1 wherein the smaller tablet containing the NSAID is enteric coated.

3. A pharmaceutical tablet as in Claim 1 or 2 wherein the NSAID is piroxicam.

4. A pharmaceutical tablet as in Claim 1 or 2 wherein the NSAID is selected from diclofenac and salts thereof.

5. A pharmaceutical tablet as in Claim 3 wherein the amount of piroxicam is from about 10 mg to about 20 mg.

6. A pharmaceutical tablet as in Claim 4 wherein the amount of diclofenac or a salt thereof is from about 25 mg to about 75 mg.

7. A pharmaceutical tablet as in any of Claims 1 to 6 wherein the amount of misoprostol is about 200 μg.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00541

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/557 A61K31/54 A61K9/20 A61K9/28
//(A61K31/557,31:54,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X, Y	EP 0 864 324 A (BASF AG) 16 September 1998 (1998-09-16) the whole document ---	1-6
X,Y	DE 196 37 479 A (BASF AG) 19 March 1998 (1998-03-19) the whole document ---	1-6
X,Y	WO 98 10752 A (BREITENBACH JOERG ;BASF AG (DE); KLEINKE ANDREAS (DE); ROSENBERG J) 19 March 1998 (1998-03-19) the whole document ---	1-6
X,Y	US 5 601 843 A (GIMET RENE A ET AL) 11 February 1997 (1997-02-11) cited in the application the whole document --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 1999	23/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fischer, W

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 99/00541

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9534291 A		DE 69508580 D	29-04-1999
		EP 0765157 A	02-04-1997
		ES 2131318 T	16-07-1999
		FI 965003 A	13-12-1996
		NO 965381 A	13-02-1997
		NZ 288185 A	26-02-1998
WO 9818610 A	07-05-1998	AU 4991597 A	22-05-1998
		EP 0935523 A	18-08-1999
		NO 992036 A	28-04-1999
EP 0465234 A	08-01-1992	AU 656140 B	27-01-1995
		AU 8014091 A	09-01-1992
		CA 2046079 A	04-01-1992
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US 5015481 A	14-05-1991	NONE	
WO 9715319 A	01-05-1997	AU 7271996 A	15-05-1997
US 5232704 A	03-08-1993	NONE	
DE 19602757 A	31-07-1997	AU 1594897 A	20-08-1997
		BR 9707083 A	23-03-1999
		CA 2243964 A	31-07-1997
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		CZ 9802320 A	14-10-1998
		WO 9726867 A	31-07-1997
		EP 0877605 A	18-11-1998
		NO 983437 A	28-09-1998
		PL 328157 A	18-01-1999
		ZA 9700596 A	24-07-1998

ATENT COOPERATION TRE. TY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 February 2000 (08.02.00)	
International application No. PCT/CA99/00541	**Applicant's or agent's file reference** PCT-1044
International filing date (day/month/year) 10 June 1999 (10.06.99)	**Priority date** (day/month/year) 15 June 1998 (15.06.98)
Applicant SHERMAN, Bernard, Charles	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

07 January 2000 (07.01.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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Authorized officer

Jean-Marc Vivet

Telephone No.: (41-22) 338.83.38

CLAIMS:

1. A pharmaceutical tablet in which are imbedded two smaller tablets, one of which comprises an NSAID and the other of which comprises misoprostol.

2. A pharmaceutical tablet as is Claim 1 wherein the NSAID is piroxicam.

3. A pharmaceutical tablet as in Claim 1 wherein the NSAID is selected from diclofenac and salts thereof.

4. A pharmaceutical tablet as in Claim 2, wherein the amount of piroxicam is from about 10 mg to about 20 mg.

5. A pharmaceutical tablet as in Claim 3, wherein the amount of diclofenac or a salt thereof is from about 25 mg to about 75 mg.

6. A pharmaceutical tablet as in any of Claims 1 to 5, wherein the amount of misoprostol is about 200 μg.

IN THE EUROPEAN PATENT OFFICE

Our Ref: ON-1375000

International Patent
Application No.: PCT/CA99/00541 Classification No.: A61K31/557

Applicant: BERNARD CHARLES SHERMAN

Agent: Ivor M. Hughes
175 Commerce Valley Dr., West, Suite 200
Thornhill, Ontario
Canada L3T 7P6

Title: PHARMACEUTICAL TABLETS COMPRISING AN NSAID AND A PROSTAGLANDIN

Inventors: BERNARD CHARLES SHERMAN

Examiner: M.D. Simm

International Filing Date: June 10, 1999 **Due Date: June 30, 2000**

May 25, 2000

VIA FACSIMILE: 011-49-89-2399-7421
ORIGINAL VIA COURIER

European Patent Office
Erhardtstrasse 27
Munich, Germany
D-80298

Dear Examiner Simm:

This letter is in response to the Written Opinion, PCT Rule 66, issued March 30, 2000 and due for response June 30, 2000. This response is also further to our discussions of May 24th and 25th, and the draft submissions forwarded May 23rd and 24th, 2000. In response to the outstanding action, Applicant encloses new pages bearing claims 1 - 7 which pages of claims the Applicant requests the Examiner to substitute for the pending claims in the application (inadvertently referred to in the Written Opinion as claims 1 - 8 but which, in reality, are only claims 1 - 6).

Reconsideration of the claims, as amended, is requested in view of the following submissions.

The Examiner has determined that the closest piece of prior art is U.S. Patent 5,601,843 which was cited in Applicant's application. This patent purports to teach a pharmaceutical composition including a core of an NSAID selected from diclofenac and piroxicam which core is surrounded by a mantle coating of a Prostaglandin wherein an intermediate coating may be present between the NSAID core and the Prostaglandin mantle coating. In other words, the mantle coating surrounds, and is concentric with, the core. In the said U.S. patent at column 1, lines 49 - 62 the following appears:

> While prostaglandins are beneficial compounds and have found therapeutic usage, prostaglandins are generally considered highly unstable. Therefore, it is desirable to find prostaglandins with the desired anti-ulcerogenic properties and which can be stabilized or provided in stabilized formulations especially with respect to contemplated oral methods of delivery.
>
> It would be desirable to provide a pharmaceutical composition which would exhibit the beneficial properties of an NSAID and which composition would exhibit the beneficial properties of a prostaglandin for countering (by inhibiting, reducing or preventing) the ulcerogenic side effects attendant to NSAID administration.

According to the said U.S. patent:

> A mantle coating 14 surrounds the inner NSAID core and encapsulates the NSAID. The mantle coating includes a prostaglandin and more preferably an orally available prostaglandin. (column 4, lines 55 - 58)

It is clear, given the state of the art prior to 1990, that the only method contemplated by this patent is by providing a core of an NSAID surrounded entirely by a mantle of prostaglandin. This U.S. patent issued February 11, 1997.

In Applicant's application Applicant discusses the problems with the administration of an NSAID and states at page 1, lines 26 - 30:

> It is desirable to provide a pharmaceutical composition which exhibits the beneficial properties of an NSAID and which also exhibits the beneficial properties of misoprostol for countering the ulcerogenic side-effects attendant to said NSAID administration.

According to the application the NSAID and misoprostol are combined in a single pharmaceutical tablet. However, according to the application:

> This is not easy to do because misoprostol is highly unstable, and it is thus desirable not to have the misoprostol and NSAID mixed together, so as to prevent any deleterious effect of the NSAID on the stability of the misoprostol. (page 2, lines 1 - 6)

The application then goes on to discuss the reference relied on by the Examiner and states that while this U.S. patent accomplishes its objective of separating the NSAID from the misoprostol, it has certain disadvantages. Two of them have been provided in the application.

> One disadvantage is the need to have a coating on the inner core in order to completely prevent contact between the NSAID and the inner core and the misoprostol in the mantle. (page 2, lines 19 - 21)

The reason is that the two of them would be in intimate contact over a substantial surface if the enteric coating were not present, i.e. the inner surface of the mantle engaging the outer surface of the core.

The second disadvantage of the teachings of the U.S. Patent 5,601,843:

> ... is that the misoprostol is dispersed throughout the mantle, and is thus exposed to the environment of the surface of the tablet. This exposure increases the vulnerability of the misoprostol to degradation due to the effects of light or atmospheric oxygen and moisture. (page 2, lines 23 - 26)

The Applicant has, in a simple manner, been able to provide a pharmaceutical formulation which takes into account all of the objectives of the prior art including U.S. Patent 5,601,843 and overcomes both disadvantages discussed above. This is accomplished by preparing two separate small tablets, the first tablet comprising the NSAID and the second comprising misoprostol, and then embedding them within a shell of pharmaceutical excipients surrounding the two tablets to make a larger pharmaceutical tablet. This is accomplished by placing part of the powder or granular mix of excipients of which the shell is to be comprised into the die punch and by then inserting the two tablets into the die and then adding the balance of the powder or granular mix of which the shell is to be comprised to cover the two smaller tablets and encase the two smaller tablets. The upper punch is then inserted into the die, as would be understood by persons skilled in the art, to compress the powder or granular mix around the two smaller caplets into the form of the final pharmaceutical tablet. The upper punch is then withdrawn.

In one embodiment the tablet containing the diclofenac or salt thereof will be coated with an enteric film coating to prevent the diclofenac or salt thereof from dissolving until after it has passed through the stomach and entered the intestine. The two tablets would, when inserted into the die punch containing a portion of the shell material, however be expected by persons skilled in the art to fall into the loose excipient material and be separately imbedded in the pockets created in the excipient material and be separated from one another by excipient material. Even if a portion of the two tablets are in contact the contact would be very small (e.g. a line or point contact). A person skilled in the art would therefore appreciate that there will be minimal contact between the two tablets in the larger pharmaceutical tablet irrespective of the process of manufacture. When the preferred enteric film coating is provided surrounding the NSAID tablet, there will be no contact. Thus, persons skilled in the art reading the application will appreciate that when the two

tablets are inserted into the die, there would be little affect (if any) on one another. Thus, given the state of the claims as they have been presented with this response there is no inconsistency between the description and claims regarding apparent features disclosed in the disclosure and included in the claims as discussed in the Examiner's observations under the heading "Certain observations of the international application".

The pharmaceutical tablets claimed in the claims presently submitted with this response clearly differentiate from the prior art formulation in U.S. Patent 5,601,843. The only solution contemplated by the said U.S. patent (the closest prior art) was one of concentric layering. However there were still disadvantages to this approach. By means of what appears to be a simple straightforward pharmaceutical tablet formulation Applicant has been able to provide a different formulation which overcomes the disadvantages of the prior art. The Examiner states that Applicant's:

> ... solution is to cover both tablets with a shell (see page 3, lines 21 - 24 and page 5, lines 11 - 15) which is constituted of usual tablet excipients. It appears that the skilled person in wishing to separate or protect one substance would simply use such coating. An example of that is shown in D1 where in order to separate both active principles an *[sic]* coating constituted of normal excipients is used.

Thus the Examiner concludes that:

> The solution is considered to be obvious in respect of D1 and in view of the normal procedures in the art.

However, with all due respect, the Examiner has used hindsight and the apparent simplicity of Applicant's solution to reject the claims. The Examiner is not entitled in law to take this position. The reason Applicant submits that the Examiner has used

a hindsight approach is because the Examiner has, without any reference in the prior art to the use of two tablets imbedded in another tablet, stated that:

> The solution is to cover both tablets with a shell.

The Examiner would only know to use both tablets imbedded in a layer of the surrounding tablet from Applicant's application.

For the purposes of the international preliminary examination (Article 33):

> (3) ... a claimed invention shall be considered to involve an inventive step if, having regard to the prior art as defined in the Regulations, it is not, at the prescribed relevant date, obvious to a person skilled in the art.

In this regard, because this PCT application is being examined under substantive European patent law, the Examiner is referred to Article 56, Inventive Step, which provides:

> An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art.

The Examiner has relied on one piece of prior art to establish the state of the art. There is no teaching of two tablets; only the teaching of two concentric layers separated by an enteric coated layer. This approach creates disadvantages. Applicant's invention claimed in its application overcomes these disadvantages in a "simple" way. In this regard, Applicant draws the attention of the Examiner to Decision T 106/84 *Re Michaelsen, Ole, Voldby*. In the case, although unrelated to pharmaceuticals, the Examiner took the position that the simplicity of the solution negated inventive step. The Technical Board of Appeal reversed the decision of the Examiner because the Applicant was able to show unexpected utility, that the problem had been attempted to be solved by others and the prior art took a different

direction. The same conclusions in Applicant's respectful submission, should be reached in this case.

In Applicant's respectful submission, even before the teaching of U.S. Patent 5,601,843, it was known that:

> Certain prostaglandins have been shown to prevent NSAID induced ulcers. (column 1, lines 39 and 40 of U.S. Patent 5,601,843)

Because of the problems with the prior art which existed before U.S. Patent 5,601,843 a pharmaceutical composition which exhibited beneficial properties was found as comprising the concentric coating of layers taught and claimed in U.S. Patent 5,601,843. Nothing else is contemplated by the prior art or this U.S. patent which the Examiner identified as the closest reference. The Examiner has not found anything more pertinent than this reference. The Examiner has not found any prior art that teaches Applicant's claimed compositions. Instead the Examiner with 20/20 hindsight states that the solution is to cover <u>both</u> tablets with a shell. This conclusion proceeds on the basis that two tablets are contemplated in the prior art to be <u>imbedded</u> in a shell to form one pharmaceutical tablet in which the two smaller tablets are <u>imbedded</u>. As there is no such basis, there is no foundation in the prior art. Thus the Examiner has arrived at a conclusion which the Examiner cannot make in law. In this regard, Applicant once again refers to the decision in T 106/84 and page 6 thereof, paragraph 8.7 which reads as follows;

> 8.7 Without question, the appellant has been successful in achieving the utmost simplicity with the self-regulating heating edge proposed by doing away with the conventional ohmic resistance heating combined with the complicated control circuitry hitherto deemed essential in the foil cutting art. <u>Achieving simplicity without the sacrifice of quality is indicative of greater rather than less inventive accomplishment</u>, even though in engineering simplification represents a particular and incessant endeavour. In fact, experience in engineering shows that it is far more difficult to develop a simple solution than a complicated one effecting the same result. <u>This is even more so when a superior result ought to</u>

> be obtained. Unfortunately, there is a danger that this will be disregarded in the appraisal of non-obviousness of simpler solutions and the statement in hindsight that such solution is so simple that anyone confronted with the problem could easily have thought of it is, indeed, the foundation of many decisions destroying applications or patents for lack of 'inventive step', even when persons with practical experience in the relevant industry recognize that it is very surprising that no-one had ever hit upon the simple solution before.

In Applicant's respectful submission, Applicant's invention involves elements each of which may be known but which together form the unexpected solution to a problem with the prior art. Applicant is not claiming exclusive rights with respect to a tablet. Applicant is claiming the unique combination which gives the unexpected benefits and overcomes the disadvantages of the prior art. This superior result has been disregarded by the Examiner. Unfortunately, in Applicant's respectful submission, the Examiner has fallen into the very trap described by the Board of Appeals:

> Unfortunately, there is a danger that this will be disregarded in the appraisal of non-obviousness of simpler solutions and the statement in hindsight that such solution is so simple that anyone confronted with the problem could easily have thought of it ....

That is precisely what has happened in this case. Applicant has "hit upon the most simple solution" to a problem exemplified by the prior art.

In view of the above submissions Applicant respectfully requests that the Examiner reconsider the position in the Written Opinion and issue a favourable Examination Report.

Examiner Simm is thanked for her time and efforts in assisting Applicant and his Agent in this matter.

If Applicant can be of further assistance, the Examiner is respectfully requested to contact Applicant's Representative, Ivor M. Hughes, at (905) 771-6414 collect at his/her convenience or fax Mr. Hughes at (905) 771-6420, any queries that can be answered by Applicant.

Respectfully submitted,

Ivor M. Hughes
Agent for Applicant

IMH/mse
Enclosures: New Claims 1 - 7

CLAIMS:

1. A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by material of the shell of the pharmaceutical tablet, one of which tablet comprises an NSAID and the other of which tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment of the surface of the pharmaceutical tablet.

2. The pharmaceutical tablet of Claim 1 wherein the smaller tablet containing the NSAID is enteric coated.

3. A pharmaceutical tablet as in Claim 1 or 2 wherein the NSAID is piroxicam.

4. A pharmaceutical tablet as in Claim 1 or 2 wherein the NSAID is selected from diclofenac and salts thereof.

5. A pharmaceutical tablet as in Claim 3 wherein the amount of piroxicam is from about 10 mg to about 20 mg.

6. A pharmaceutical tablet as in Claim 4 wherein the amount of diclofenac or a salt thereof is from about 25 mg to about 75 mg.

7. A pharmaceutical tablet as in any of Claims 1 to 6 wherein the amount of misoprostol is about 200 μg.

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/557, 31/54, 9/20, 9/28 // (A61K 31/557, 31:54, 31:195)

A1

(11) International Publication Number: WO 99/65496

(43) International Publication Date: 23 December 1999 (23.12.99)

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(22) International Filing Date: 10 June 1999 (10.06.99)

(30) Priority Data:
2,241,342 15 June 1998 (15.06.98) CA

(71)(72) Applicant and Inventor: SHERMAN, Bernard, Charles [CA/CA]; 50 Old Colony Road, Willowdale, Ontario M2L 2K1 (CA).

(81) Designated States: AU, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: PHARMACEUTICAL TABLETS COMPRISING AN NSAID AND A PROSTAGLANDIN

(57) Abstract

A pharmaceutical tablet which incorporates two smaller tablets, one of which comprises an NSAID and the other of which comprises misoprostol.

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PHARMACEUTICAL TABLETS COMPRISING AN NSAID AND A PROSTAGLANDIN

BACKGROUND OF THE INVENTION

The invention herein is directed to a pharmaceutical tablet which comprises both an NSAID and misoprostol.

Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise a class of drugs which have long been recognized as having high therapeutic value especially for the treatment of inflammatory conditions such as exhibited in inflammatory diseases like osteoarthritis and rheumatoid arthritis. While the NSAIDs present a beneficial therapeutic value, they also exhibit undesirable side effects. An especially undesirable side effect of the administration of NSAIDs is the ulcerogenic effects generally associated with chronic use. NSAID induced ulcers in the stomach can be dangerous. Such ulcers generally exhibit few or no symptoms and may cause dangerous bleeding when undetected. In some instances, bleeding ulcers can prove fatal.

Certain prostaglandins have been shown to prevent NSAID induced ulcers. Misoprostol is a prostaglandin which has been accepted for use in the treatment of NSAID induced ulcers in many countries, including the United States.

It is desirable to provide a pharmaceutical composition which exhibits the beneficial properties of an NSAID and which also exhibits the beneficial properties of misoprostol for countering the ulcerogenic side effects attendent to NSAID administration.

This can be achieved by combining an NSAID and misoprostol in a single pharmaceutical tablet. However this in not easy to do, because misoprostol is highly unstable, and it is thus desirable not to have the misoprostol and NSAID mixed together, so as to prevent any deleterious effect of the NSAID on the stability of the misoprostol.

One solution to this problem, which is disclosed in US Patent 5601843, is to produce a tablet consisting of an inner core which comprises the NSAID and a mantle which surrounds the inner core and comprises the misoprostol. It is also disclosed that, in order to prevent contact between the misoprostol and the NSAID at the surface of the inner core, the inner core may be coated with an inert coating. Such coating may be an enteric coating, which also serves to reduce the likelihood of the NSAID dissolving in the stomach and thereby prevent exposing the stomach to the NSAID.

While the invention of US Patent 5601843 accomplishes its objective of separating the NSAID from the misoprostol, it has certain disadvantages. One disadvantage is the need to have a coating on the inner core in order to completely prevent contact between the NSAID in the inner core and the misoprostol in the mantle.

A second disadvantage is that the misoprostol is dispersed throughout the mantle, and is thus exposed to the environment at the surface of the tablet. This exposure increases the vulnerability of the misoprostol to degradation due to the effects of light or atmospheric oxygen and moisture.

The object of the present invention is to enable a pharmaceutical tablet that incorporates both an NSAID and misoprostol, but overcomes these disadvantages.

BRIEF SUMMARY OF THE INVENTION

The present invention is a pharmaceutical composition in the form of a tablet in which two smaller tablets are embedded, one of which comprises an NSAID and the second of which comprises misoprostol.

DETAILED DESCRIPTION OF THE INVENTION

Pharmaceutical tablets are routinely made on a tablet press. In the tabletting process, a mixture of materials in the form of a free flowing powder or granular mix is filled into a metal die, into which a metal punch protrudes from beneath. A second metal punch is then inserted into the die from above, and pressure is applied to the upper and lower punches to cause the powder or granular mix to be compressed into a tablet. The upper punch is then withdrawn, and the tablet is ejected from the die by raising the lower punch further into the die.

Compositions (i.e. tablets) of the present invention may be made as follows:

1. Firstly, a tablet comprising the NSAID and a tablet comprising the misoprostol are made in separate tabletting operations. The portion of the composition which surrounds the two smaller tablets will be referred to herein as the "shell".

2. Then the final composition is assembled in a further tabletting operation as follows:

   (i) Part of the powder or granular mix of which the shell is to be comprised is filled into the die, into which a punch has been inserted from below.

(ii) One of the smaller tablets comprising the NSAID and one of the smaller tablets comprising the misoprostol are then inserted into the die.

(iii) The balance of the powder or granular mix of which the shell is to be comprised is then filled into the die to cover two smaller tablets.

(iv) The upper punch is then inserted into the die from above and pressure is applied between the punches to compress the powder or granular mix around the two smaller tablets into the form of the final tablet.

(v) The upper punch is then withdrawn and the lower punch is raised further into the die to eject the composition.

The NSAID contained within one of two smaller tablets will preferably be piroxicam or diclofenac or a salt of diclofenac such as diclofenac sodium or diclofenac potassium. Most preferably, the NSAID will be diclofenac sodium.

Where diclofenac or a salt thereof is used, the amount per tablet will preferably be from 25 to 75 mg. The tablet containing diclofenac or salt thereof will contain, along with the diclofenac or salt thereof, usual tablet excipients such as binders, lubricants, fillers and the like. Preferably, the tablet containing the diclofenac or salt thereof will be coated with an enteric film coating to prevent the diclofenac or salt thereof from dissolving until after it has passed through the stomach and entered the small intestine. The enteric coating can be formulated with any suitable enteric coating polymer, many of which are known to those skilled in the art.

Where piroxicam is used as the NSAID, the amount per tablet will preferably be 10 to 20 mg. Again the tablet containing piroxicam will also comprise usual tablet excipients.

The tablet containing the misoprostol will also include, along with the misoprostol, usual tabletting excipients. The misoprostol will preferably be used in the form of a dispersion in hydroxypropyl methylcellulose, which is known in the prior art to improve the stability of misoprostol. The quantity of misoprostol per tablet will preferably be about 200 μg.

The shell which surrounds the tablet containing the NSAID and the tablet containing the misoprostol will be comprised of usual tablet excipients, without any active medicinal ingredient mixed therein.

The invention will be further understood from the following example, which is intended to be illustrative and not limiting of the scope of the invention.

EXAMPLE 1

Tablets containing diclofenac sodium are made with a composition as follows:

	Amount per tablet
Diclofenac sodium	50.0 mg
Microcrystalline cellulose	24.0 mg
Magnesium stearate	1.0 mg
Croscarmellose sodium	5.0 mg
	80.0 mg

These cores are then optionally enteric coated by spraying onto them a suspension or solution of an enteric coating polymer and a plasticizer.

EXAMPLE 2

Tablets containing misoprostol are made with a composition as follows:

	Amount per tablet
Misoprostol 1% dispersion in hydroxypropyl methylcellulose	20.0 mg
Microcrystalline cellulose	8.5 mg
Magnesium stearate	0.5 mg
Croscarmellose sodium	1.0 mg
	30.0 mg

EXAMPLE 3

A powder mix for producing the shell of the final tablet is prepared as a mixture of 99.5% by weight microcrystalline cellulose and 0.5% magnesium stearate.

EXAMPLE 4

The final composition is then made by making tablets from the mix of Example 3 and embedding in each such tablet one tablet from Example 1 and one tablet from Example 2, by the procedure previously described; that is to say, using a tablet press equipped to insert one tablet from Example 1 and one tablet from Example 2 as well as a quantity of the powder mix for the shell from Example 3 into a die, and making the final tablet by compression between a lower punch and a upper punch inserted into the die from below and above respectively.

CLAIMS:

1. A pharmaceutical tablet in which are imbedded two smaller tablets, one of which comprises an NSAID and the other of which comprises misoprostol.

2. A pharmaceutical tablet as is Claim 1 wherein the NSAID is piroxicam.

3. A pharmaceutical tablet as in Claim 1 wherein the NSAID is selected from diclofenac and salts thereof.

4. A pharmaceutical tablet as in Claim 2, wherein the amount of piroxicam is from about 10 mg to about 20 mg.

5. A pharmaceutical tablet as in Claim 3, wherein the amount of diclofenac or a salt thereof is from about 25 mg to about 75 mg.

6. A pharmaceutical tablet as in any of Claims 1 to 5, wherein the amount of misoprostol is about 200 μg.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00541

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/557 A61K31/54 A61K9/20 A61K9/28
//(A61K31/557,31:54,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X, Y	EP 0 864 324 A (BASF AG) 16 September 1998 (1998-09-16) the whole document ---	1-6
X,Y	DE 196 37 479 A (BASF AG) 19 March 1998 (1998-03-19) the whole document ---	1-6
X,Y	WO 98 10752 A (BREITENBACH JOERG ;BASF AG (DE); KLEINKE ANDREAS (DE); ROSENBERG J) 19 March 1998 (1998-03-19) the whole document ---	1-6
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 1999	23/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fischer, W

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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International Application No
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PCT-1044		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00541	10/06/1999	15/06/1998
International Patent Classification (IPC) or national classification and IPC A61K31/557		
Applicant SHERMAN, Bernard, Charles		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07/01/2000	06.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Simm, M.D. Telephone No. +49 89 2399 7411

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00541

I. Basis of the r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-6	as originally filed			

Claims, No.:

1-7	as received on	29/05/2000	with letter of	25/05/2000

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-7
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: US-A-5 601 843 (GIMET RENE A ET AL) 11 February 1997 (1997-02-11) cited in the application

Inventive Step (Art 33(3) PCT)

The document D1, acknowledged on page 2 second paragraph of the present application, is considered to be the closest prior art. Claim 1 differs from the teachings of D1 in that the two tablets, one comprising an NSAID and the other comprising misoprostol, are embedded in a pharmaceutical tablet covered by material of the shell of the pharmaceutical tablet.

The technical effect provided by this technical feature is that the misoprostol is protected from the environment (see page 2, lines 23-30).
The technical problem to be solved by the present application regarding the closest prior art is to provide the tablet of D1 with a protection from the environment (see page 2, lines 23-30).

The solution is to cover both tablets with a shell (see page 3, lines 21-24 and page 5, lines 11-15) which is constituted of usual tablet excipients.

This solution is not disclosed in the cited prior art. Thus, it appears that present claim 1 is novel and involves an inventive step.

The features of dependent claims 2-8 are disclosed in D1 (see claims 1 and 5) or are the results of normal procedures in the art.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PCT-1044		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/ 00541	10/06/1999	15/06/1998
Applicant		
SHERMAN, Bernard, Charles		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
T/CA 99/00541

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/557 A61K31/54 A61K9/20 A61K9/28
//(A61K31/557,31:54,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X, Y	EP 0 864 324 A (BASF AG) 16 September 1998 (1998-09-16) the whole document ---	1-6
X,Y	DE 196 37 479 A (BASF AG) 19 March 1998 (1998-03-19) the whole document ---	1-6
X,Y	WO 98 10752 A (BREITENBACH JOERG ;BASF AG (DE); KLEINKE ANDREAS (DE); ROSENBERG J) 19 March 1998 (1998-03-19) the whole document ---	1-6
X,Y	US 5 601 843 A (GIMET RENE A ET AL) 11 February 1997 (1997-02-11) cited in the application the whole document ---	1-6

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 1999	23/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fischer, W

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
T/CA 99/00541

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 91 16886 A (SEARLE & CO) 14 November 1991 (1991-11-14) the whole document	1-6
X,Y	WO 91 16895 A (SEARLE & CO) 14 November 1991 (1991-11-14) the whole document	1-6
Y	WO 95 34291 A (DUMEX LTD AS ;NORLING TOMAS (DK); JENSEN LONE NOERGAARD (DK); HANS) 21 December 1995 (1995-12-21) the whole document	1-6
Y	WO 98 18610 A (LENGERICH BERNHARD H VAN) 7 May 1998 (1998-05-07) figure 4	1
A	EP 0 465 234 A (MCNEIL PPC INC) 8 January 1992 (1992-01-08)	
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 99/00541

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